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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,489	02/21/2006	Matthew Scanlan	029065.51088US2	3837

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EXAMINER

NATARAJAN, MEERA

ART UNIT	PAPER NUMBER
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1643

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11/30/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/532,489	Applicant(s) SCANLAN ET AL.	
	Examiner Meera Natarajan	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 September 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 6-19, 21-23, 25-31 and 33-47 is/are pending in the application.
- 4a) Of the above claim(s) 8, 9, 21-23, 30, 33, 34 and 41-47 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 6, 7, 25-31 and 35-44 is/are rejected.
- 7) ☐ Claim(s) 45-47 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The amendment filed 09/04/2007 is acknowledged and entered into the record.
2. Claims 6-19, 21-23, 25-31, 33-47 are currently pending.
3. Claims 1-4 have been cancelled without prejudice by Applicant.
4. Claims 8, 9, 21-23, 30, 33, 34, 41-47 have been withdrawn as being drawn to nonelected inventions and species.
5. Claims 6, 7, 25-31, 35-47 will be examined on the merits.

Election/Restrictions

6. After further consideration, the species requirement for SEQ ID NO: of CDR3 made in the office action mailed 01/25/2007 has been withdrawn. All species will be examined on the merits.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 6, 7, 25-31, 35-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a substantially pure immunoglobulin molecule which binds specifically to A34 antigen, wherein said immunoglobulin molecule comprises the combinations of CDR1, 2, and 3 for each the light and heavy

Art Unit: 1643

chain (antibody clones 209-970, 209-564, 209-342) as listed in Fig. 24, does not reasonably provide enablement for a substantially pure immunoglobulin molecule which binds specifically to A34 antigen, wherein said immunoglobulin molecule comprises **at least** one CDR or **any combinations** of CDRs thereof of the SEQ ID NOs: listed in Claims 39, 40, and 41. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

9. In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

10. The claims are drawn to an immunoglobulin molecule which binds specifically to A34 antigen, wherein said immunoglobulin molecule comprises (A) at least one variable region comprising at least one CDR sequence selected from SEQ ID NO: 32-49, (B) a heavy chain variable region comprising three CDR regions and **any** combinations thereof of SEQ ID NOs: 35, 36, 37, 41, 42, 43, 47, 48, and 49, and (C) a light chain

Art Unit: 1643

variable region comprising three CDR regions and **any** combinations thereof of SEQ ID NOs: 32, 33, 34, 38, 39, 40, 44, 45 and 46.

11. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. MacCallum et al. J. Mol. Biol. (1996) 262, 732-745, analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as

Art Unit: 1643

important in defining canonical backbone conformations (see page 735, left col.).

Pascalis et al. *The Journal of Immunology* (2002) 169, 3076-3084 demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.). The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset et al. (2003) *BBRC* 307, 198-205, which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al. also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left col.). Vajdos et al. (2002) 320, 415-428, additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.). Holm et al. (2007) 44, 1075-1084 describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract).

Art Unit: 1643

Chen et al. J. Mol. Bio. (1999) 293, 865-881. describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866). Wu et al. J. Mol. Biol. (1999) 294, 151-162. state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

The references demonstrate that an antibody must comprise all 6 CDRs in order to maintain the antigen binding specificity and affinity which is characteristic of the immunoglobulin.

12. In addition, Claims 39, 40, and 41 are broadly drawn to an immunoglobulin comprising **any combination** of CDRs. The claims as written are drawn to an antibody comprising a heavy or light chain variable region with 3 CDR's of any combination of SEQ ID NOs listed. This would include chains comprising two CDR1 regions and one CDR3 region or two CDR2 regions and one CDR3 region and the pairing of a heavy chain of one antibody to the light chain of another antibody. The specification does not provide support for the finite number of various combinations of the CDRs other than the combinations listed in Fig. 24 for clones 342, 564, and 970 which identify all 3 CDRs for each heavy and light chain variable region for each clone. Undue experimentation would be required in order to determine what combinations of the CDRs would result in a functional antibody.

All other objections and rejections are withdrawn in view of the applicant's amendments and arguments thereto as set forth in the paper filed 09/04/2007.

Conclusion

13. Claims 6, 7, 25-31, 35-44 are rejected.
14. Claims 45-47 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.
15. No Claim is allowed.
16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Meera Natarajan whose telephone number is 571-270-3058. The examiner can normally be reached on Monday-Thursday, 8:30AM-6:00PM, ALT. Friday. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you

Art Unit: 1643

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MN



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SUPERVISORY PATENT EXAMINER